

REMARKS

By the present amendment, claims 25, 28, 29, 32, 35-41, and 45 have been amended to obviate the examiner's objections thereto and/or to further clarify the concepts of the present invention. Entry of these amendments is respectfully requested.

In the Office Action, claims 25-46 were rejected under the second paragraph of 35 U.S.C. §112 as being indefinite, primarily that various terms and phrases as noted did not precisely define the invention. In particular, the following informalities were alleged and applicants' response thereto is set forth thereafter:

(1) Claim 25 was alleged to be indefinite for the use of the phrase "of the general formula" and it was suggested that "of formula (2)" be used. As can be noted from the claim amendments herein, the suggestion of the examiner has been adopted.

(2) Claim 25 was alleged not to use active language appropriate for a method claim and revision was requested. The suggested language of "comprising, crystallizing" has been adopted.

(3) Claim 28 was alleged to be indefinite for the use of the phrase "represented by the following general formula" since it was unclear whether formula (1) or another formula was intended. Further, it was asserted that X was not defined. As can be noted from the claim amendments herein, the claim now recites "the following formula (1)." In addition, X has been defined in the claim in accordance with page 1, line 13 and page 5, line 10 of the subject specification.

(4) Claims 28 and 29 were objected to for the use of the term "dominant" since it was alleged that this term was not interpretable in the context of the claim. As can be noted from the claim amendments herein, the term has been replaced by the term "major" in both claims.

(5) Claim 28 was alleged to be indefinite for the use of the phrase "represented by the following general formula" since it was unclear whether formula (1) or another formula was intended. As can be noted from the claim amendments herein, the claim now recites "the following formula (1)."

(6) Claims 32 and 35-38 were objected to for the use of the phrase "is obtainable by diastereo-selective reduction..." as it was asserted that the phrase does not further limit the preceding claim. As can be noted from the claim amendments herein, the suggestion of the examiner to utilize "is obtained" has been adopted in claims 32 and 35-38.

(7) Claims 39 and 40 were alleged to be indefinite for the use of the phrase "giving the mixture" apparently since the phrase does not have antecedent basis. As can be noted from the claim amendments herein, the noted phrase has been replaced by the phrase "obtaining the mixture" which does have antecedent basis.

(8) Claim 41 was alleged to be indefinite for referring to "the aromatic hydrocarbon solvent" and being dependent from claim 30 where no aromatic hydrocarbon solvent is recited. As can be noted from claims 28 and 29, from which claim 41 now depends, an aromatic solvent is recited therein. Thus, the claim does have proper antecedent basis.

(9) Claim 43 was alleged to be indefinite for stating that the aliphatic hydrocarbon is methyl cyclohexane since it was asserted that this compound is not an aliphatic hydrocarbon.

Contrary to the assertion made in the Action, methylcyclohexane is an aliphatic hydrocarbon. The term "aliphatic hydrocarbon" generally includes cyclic and acyclic hydrocarbons, but excludes aromatic hydrocarbons. In support thereof, attention is directed to the attached copies of Cram, Fundamental Organic Chemistry and Encyclopedic Dictionary of Chemistry, as well as translations thereof.

(10) Claim 45 was alleged to be indefinite for the use of the phrase "of the general formula." As can be noted from the claim amendments herein, the claim now recites "the following formula (4)" or "the following formula (5)."

For the reasons set forth above, withdrawal of the rejection under the second paragraph of 35 U.S.C. § 112 is respectfully requested.

Applicants acknowledge with appreciation the indication that the claims are free from the art. Thus, since the above rejection has been obviated by the amendments and submissions herein, it is submitted that the application is now allowable.

In view of the foregoing, it is submitted that the subject application is now in condition for allowance and early notice to that effect is earnestly solicited.

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In the event this paper is not timely filed, the undersigned hereby petitions for an appropriate extension of time. The fee for this extension may be charged to Deposit Account No. 01-2340, along with any other additional fees which may be required with respect to this paper.

Respectfully submitted,

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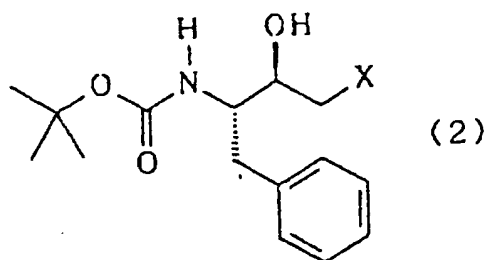
Enclosures: as indicated in item (9) above

Marked Up Version of Amendments to Specification and Claims

IN THE CLAIMS:

Amend the claims as follows:

25. (Amended) A purification/isolation method of a (2R,3S)-1-halo-2-hydroxy-3-N-(tert-butoxycarbonyl) amino-4-phenylbutane of the following ~~general~~ formula (2):



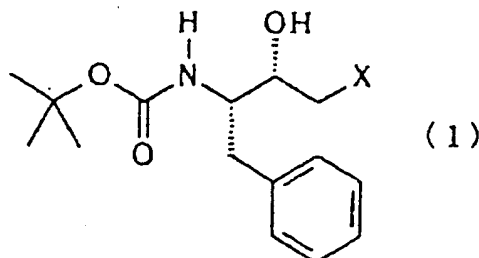
wherein X represents a halogen atom

which comprises, for the purpose of removing contaminant impurity from a mixture containing (2R,3S) -halo-2-hydroxy-3-N-(tert-butoxycarbonyl) amino-4-phenylbutane (2),

causing crystallizing the compound (2) ~~to be crystallized~~ in the presence of an aliphatic hydrocarbon solvent

and collecting the obtained crystals.

28. (Amended) The purification/isolation method according to Claim 25, 26 or 27 which comprises causing crystallizing a compound (1) represented by the following ~~general~~ formula (1):



wherein X represents a halogen atom, ~~to be crystallized~~ from a mixture containing said compound (1) and compound (2) in the presence of an aromatic hydrocarbon solvent as the ~~dominant~~ major solvent and collecting the crystals,

and then ~~causing crystallizing~~ said compound (2) ~~to be crystallized~~ by substituting an aliphatic hydrocarbon solvent for the major ~~dominant~~ solvent of the mother liquor predominantly having the residual compound (2)

and collecting the obtained crystals.

29. (Amended) A purification/isolation method of a compound (1) and a compound (2)

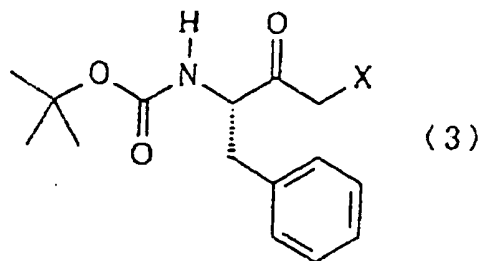
which comprises

~~causing crystallizing~~ said compound (1) ~~to be crystallized~~ from a mixture containing the compound (1) and the compound (2) in the presence of an aromatic hydrocarbon solvent as the ~~predominant~~ major solvent and collecting the crystals,

and then ~~causing crystallizing~~ said compound (2) ~~to be crystallized~~ by substituting an aliphatic hydrocarbon solvent for the ~~dominant~~ major solvent of the mother liquor predominantly having the residual compound (2).

32. (Twice Amended) The purification/isolation method according to Claim 25,26, 27, 29, or 30

wherein a mixture containing the compound (2) is obtained ~~obtainable~~ by diastereo-selective reduction of a (3S)-1-halo-2-oxo-3-N-(tert-butoxycarbonyl) amino-4-phenylbutane of the following ~~general~~ formula (3):



wherein X represents a halogen atom.

35. (Twice Amended) The purification/isolation method according to Claim 32, wherein the mixture containing the compound (2) is obtained ~~obtainable~~ by subjecting the compound (3) to diastereo-selective reduction, extracting said compound (2) from the resulting reaction mixture into an organic phase in the presence of an organic solvent and water, separating said organic phase from the aqueous phase and adjusting it to a concentration suitable for crystallization.

36. (Amended) The purification/isolation method according to Claim 35 wherein the mixture containing the compound (2) is obtained ~~obtainable~~ by subjecting compound (3) to diastereo-selective reduction, extracting the reaction mixture with a hydrocarbon solvent and concentrating the separated organic phase or extracting the reaction mixture with an organic solvent and finally substituting a hydrocarbon solvent for the solvent of the separated organic phase.

37. (Amended) The purification/isolation method according to Claim 36 wherein the mixture containing the compound (2) is obtained ~~obtainable~~ by subjecting said compound (3) to reduction, extracting the reaction mixture with an organic solvent and finally substituting an aliphatic hydrocarbon solvent for the solvent of the separated organic phase.

38. (Amended) The purification/isolation method according to Claim 37 wherein the mixture containing the compound (2) is obtained ~~obtainable~~ by subjecting said compound (3) to reduction, extracting the reaction mixture with an aromatic organic solvent and finally substituting an aliphatic hydrocarbon solvent for the solvent of the separated organic phase.

39. (Twice Amended) The purification/isolation method according to Claim 35

wherein the procedure for obtaining giving the mixture containing the compound (2) is carried out at a temperature not exceeding 60 °C.

40. (Twice Amended) The purification/isolation method according to Claim 25,26, 27 or 30

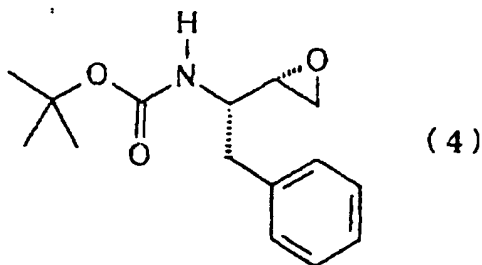
wherein the whole procedure for obtaining giving the compound (2) as crystals is carried out at a temperature not exceeding 60 °C.

41. (Amended) The purification/isolation method according to Claim ~~30 or 38~~ 28 or 29

wherein the aromatic hydrocarbon solvent is at least one member selected from the group consisting of benzene, toluene, xylene, and ethylbenzene.

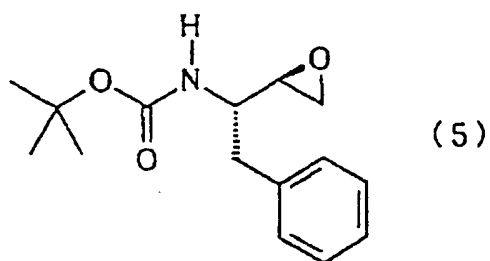
45. (Amended) The purification/isolation method according to Claim 25, 26, 27, ~~28,~~ 29, 30, ~~31,~~ 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, or 44

wherein the impurity contaminating the mixture containing the compound (2) is at least one member selected from the group consisting of said compound (1), which is the diastereomer, the compound (3), (2S,3S)-1,2-epoxy-3-N-(tert-butoxycarbonyl)amino-4-phenylbutane of the following ~~general~~ formula (4):



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and (2R,3S)-1,2-epoxy-3-N-(tert-butoxycarbonyl)amino-4-phenylbutane of the following general formula (5):



3

炭 化 水 素

3.1 分 類 Classification

炭化水素 (hydrocarbon) とは炭素と水素だけで成り立っている有機化合物のことをいう用語である。炭化水素はその構造によって定義される二つの種類に大別される。脂肪族炭化水素 (aliphatic hydrocarbons) は炭素原子の鎖をもち、その鎖が環になったものもある。もし環がなければ、それらの化合物は非環式または鎖式 (acyclic) といわれ、もし環が存在すれば、環式 (cyclic) または脂環式 (alicyclic) といわれる (32 頁)。二、三の例外的な環式化合物は別として、分子量の似ている鎖式および環式炭化水素はともにその化学的性質も物理的性質もよく似ている。芳香族炭化水素 (aromatic hydrocarbons) は脂肪族炭化水素の物理的および化学的性質とは非常に異なっており、炭素-炭素二重結合と単結合が交互に存在する環を含んでいる。たいていの一般的な芳香族炭化水素には六員環および3個の炭素-炭素二重結合と3個の単結合が交互に存在する。これらの三種の炭化水素の例を図 3.1 に掲げた。

たいていの有機化合物では比較的小数の異なった構成単位より成るが、その並び方は実に多様である。それらの構成単位は二つの大きなカテゴリーに分けられる。すなわち、炭素および水素のみなら

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The translation of Cram "Fundamental Organic Chemistry"
(Published by Hirokawa Publishing Co., on April 15, 1969)

The translation of page 25, first paragraph (lines 1 to 13):

CHAPTER 3
Hydrocarbons

3.1 Classification

The term "hydrocarbons" means organic carbons consisting exclusively of carbon and hydrogen atom. The hydrocarbons are roughly classified into two categories depending on their structures. Aliphatic hydrocarbons have carbon chains, and some of them have cyclic carbon chain structures. A hydrocarbon not having a cyclic structure is referred to as a "non-cyclic" or "acyclic" compound, whereas a hydrocarbon having a cyclic structure is referred to as a "cyclic" or "alicyclic" compound (page 32). Aside from two or three exceptional cyclic compounds, both acyclic and alicyclic hydrocarbons having similar molecular weight also have similar chemical or physical properties. On the other hand, aromatic hydrocarbons are quite different from the aliphatic compounds in chemical or physical properties, and contain cyclic structures in which carbon-carbon double bonds and single bonds are alternately existed. Most general aromatic hydrocarbons have a six-membered ring, three carbon-carbon double bonds and 3 single bonds, which are alternately existed. Examples of these three hydrocarbons are mentioned in Fig. 3.1.

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水酸基を有する炭素原子に結合したアルキル基が1個の場合第一級アルコール*, 2個の場合第二級アルコール*, 3個の場合第三級アルコール*と分類する。また、水酸基の数により一価アルコール*, 二価アルコール*, 多価アルコール*などに分類する。酸とエステルをつくり、第二級アルコールは酸化によりケトンを生じ、第一級アルコールはアルデヒドを生ずるなど、水酸基に特有の反応性を示す。

脂肪族エーテル [aliphatic ether] アルコール2分子から水分子が除かれて生じる中性の化合物の総称。一般式 ROR' で示される。RとR'が等しい単純なエーテルは、アルコールの脱水剤による脱水によって得られる。また、 ROR' 型の混合エーテルは、アルコキシド*とハロゲン化アルキルまたは硫酸アルキルとの反応によって合成される(→ウィリアムソンのエーテル合成)。一般に反応性に乏しく安定な直鎖状エーテルであるジエチルエーテルや環状エーテルであるテトラヒドロフラン、ジオキサンなどは、有機合成における溶媒として広い用途を有する。

脂肪族化合物 [aliphatic compound] 歴史的には油脂(脂肪)の代表的な成分であるパルミチン酸やステアリン酸などの炭素骨格がいずれも鎖式構造であることから、分子内に環式構造を含まず鎖式構造のみから成る有機化合物を脂肪族化合物と総称してきた。しかし、現代では芳香族化合物*以外の化合物を脂肪族化合物という場合が多い。したがって、シクロヘキサンのような環式炭化水素以外にジカルボン酸の無水物、オキシ酸のラクトンや環状エーテルなどの環式化合物をも含める。

脂肪族酸 [aliphatic acid] 脂肪族炭化水素の水素原子をカルボキシル基で置換した形の化合物で、分子中のカルボキシル基の数が1, 2, 3, 4個のものをそれぞれモノカルボン酸、ジカルボン酸、トリカルボン酸、テトラカルボン酸といい、2個以上のものを総称してポリカルボン酸という。炭素が飽和か不飽和かによって飽和カルボン酸、不飽和カルボン酸に分類される。モノカルボン酸は特に脂肪酸*とよばれている。(→カルボン酸)

脂肪族炭化水素 [aliphatic hydrocarbon] パラフィン族炭化水素(paraffin hydrocarbon)ともいう。脂肪族化合物に属する炭化水素をいい、芳香族性を有する芳香族炭化水素*と対比される。分子内の炭素骨格が鎖式構造である鎖式炭化水素のうち、炭素原子数が4以上のものには鎖式構造の形状による異性体が存在する。炭素骨格が直線状のものをノルマル(n-)系といい、枝分かれして側鎖のあるものをイソ系という。飽和炭化水素と不飽和炭化水素とがある。飽和炭化水素の同族列はメタン列炭化水素といい、n-アルカン*(n-パラフィン)とイソアルカン*(イソパラフィン)とからなる。不飽和炭化水素のうち、二重結合のあるものをエチレン列炭化水素(アルケン*, オレフィン)といい、三重結合のあるものをアセチレン列炭化水素(アルキン*)という。分子内に二重結合と三重結合の両方がある複合系をエニン系炭化水素という。一方、環式構造をもつ脂肪族炭化水素としてはシクロヘキサンやデカリンやステロイドのように芳香族性をもたないさまざまな脂環式化合物*がある。

脂肪族ニトリル [aliphatic nitrile] シアン化アルキル(alkyl cyanide)ともいう。シアノ基 $-C\equiv N$ がアルキル基Rの炭素原子に結合した化合物で、 RCN で表される。一般に、対応するカルボン酸の誘導体として接頭語にニトリルをつけて命名する(例: CH_3CN はアセトニトリル)。シアノ基を置換基として接頭語にシアノをつけて命名することもある(例: $CNCH_2CO_2H$ はシアノ酢酸)。基官能命名法ではシアン化物として命名する(例: $CH_2=CHCH_2CN$ はシアン化アリル)。製法、性質はニトリル*の項参照。

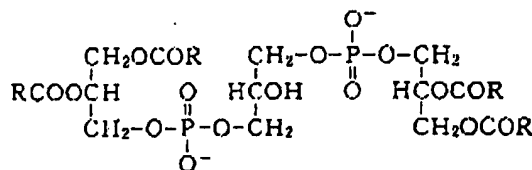
脂肪族ニトロ化合物は、あるいは四酸化二窒素による脂肪族化合物の直接ニトロ化、亜硝酸塩を用いたニトロ化、オキシムの酸化などの種々の方法によって合成される。単純ニトロアルカンは無色の液体で、水には難溶であり大部分の有機溶媒に易溶である。有機溶媒として重要である。たとえば、ニトロメタンの比誘電率は37と大きく、イオン反応の良溶媒である。UVスペクトルは一般に $\sim 210\text{ nm}$ ($\epsilon \approx 15,000$)に $\pi \rightarrow \pi^*$ 遷移の吸収を有している。 α 位に水素のある化合物は酸性を示し、アルカリ水溶液に溶ける。

脂肪族ニトロ化合物 [aliphatic nitroso compound]

→ニトロ化合物

シーボーグ Seaborg, Glenn Theodor 1912.4.19 ~
アメリカの化学者。ミシガン州イシュプリングに生まれる。1929年カリフォルニア大学ロスアンゼルス校に入学。1937年、同大学パークレー校において学位を得た。その後2年間G. N. Lewis*の助手を務め、1941年助教授。1945年から教授。1958年には学長に選ばれた。また、1961~68年まで原子力委員を務めるなど、多くの政府委員を務めた。彼はE. M. McMillan*らの共同研究者とともに94番のプルトニウムから102番までのすべての超ウラン元素*を発見し、またそれらを単離した。さらに、これらの元素の性質を研究し89番元素のアクチニウムから始まる一連の元素がランタニドに類似する電子構造をもつことを提唱し、これらをアクチニド(→アクチノイド)とよんだ。これらの業績により、1951年McMillanとともにノーベル化学賞を受けた。1942年から1946年まで、アメリカの原爆開発計画であるマンハッタン計画*に参加し、プルトニウム分離法開発のリーダーとして働いた。おもな著書には、J. J. KatzおよびW. M. Manningとの共著である"The Transuranium Elements"(1949)などがある。

ジホスファチジルグリセロール [diphosphatidylglycerol] =カルジオリピン(cardiolipin)。高等動物の臓器に総リン脂質の数パーセント含まれているが、心筋には多く十数%に達する。また植物、細菌にも見いだされている。



動物組織では主としてミトコンドリア内膜に局在し、高度不飽和脂肪酸の含量が高い。エタノール、メタノール、エーテル、石油エーテル、ベンゼン、クロロホルムに可溶。アセトン、酢酸エチルに難溶。Cd, Baとエタノール不溶性の塩をつくる。梅毒血清反応(ワッセルマン反応)の抗原物質として知られる。

ジホスファニ [diphosphane] [1] H_2P-PH_3 。分子量66.98。旧名はジホスフィン(diphosphine)。リン化カルシウムに水を加えると得られる。無色の液体。融点 $-99^\circ C$ 、沸点 $51.7^\circ C$ 。空気中で自然発火する。不安定で、光で PH_3 と $(P_2H)_2$ に分解する。CAS[13445-50-6]

[2] $RR'P-PRR'$ の一般名。相当する第二級ホスフィンとクロロホスフィンとの反応、クロロホスフィンとナトリウムとの反応などで得られる。低級アルキル(メチル、エチルなど)置換体は空気中で自然発火する。

ジホスフィン [diphosphine] =ジホスファン

ジホスホビリジンヌクレオチド [diphosphopyridine nucleotide] =ニコチンアミドアデニンヌクレオチド

ジホスホン酸 [diphosphonic acid] =二亜リン酸(diphosphorous acid)、ピロ亜リン酸(pyrophosphorous acid)。

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The translation of Encyclopedic Dictionary of Chemistry
(Published by Tokyo Kagaku Dozin, on October 20, 1989)

The translation of page 1045, lines 19 to 27:

[Aliphatic compound]

Historically, the term "aliphatic compounds" used to be a generic term to refer to organic compounds not containing a cyclic structure but consisting exclusively of acyclic structure, since any carbon skeletons of representative compounds of fat, such as palmitic acid, stearic acid, are acyclic structures. But now, the term "aliphatic compound" is mostly used to refer to organic compounds other than aromatic compound. Therefore, aliphatic compounds include not only cyclic hydrocarbons such as cyclohexane but also cyclic compounds, for example, dicarboxylic acid anhydrides, lactones of oxyacid, and cyclic ethers, and the like.

The translation of page 1045, lines 36 to 53:

[Aliphatic hydrocarbon]

It is also referred to as "paraffin hydrocarbons". The term "aliphatic hydrocarbon" means a hydrocarbon belonging to aliphatic compounds, and is contrasted with the term "aromatic hydrocarbon", which means a hydrocarbon with aromaticity. Among chain hydrocarbons whose carbon skeletons of the molecules are chain structures, those having 4 or more carbon atoms have isomers caused by the difference between forms of chain structure. One having linear carbon skeleton is referred to as "normal" (n-) hydrocarbon, and one having branched side chain as "iso" hydrocarbon. Aliphatic hydrocarbons are classified into saturated or unsaturated hydrocarbons. The homologous series of saturated hydrocarbons are referred to as "methane-series hydrocarbons", which comprise n-alkane (n-paraffin) and iso-alkane (isoparaffin). Among unsaturated hydrocarbons, those having a double bond are referred to as

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"ethylene-series hydrocarbons" (alkene, olefin), and those having a triple bond are referred to as "acetylene-series hydrocarbons" (alkyne). Hydrocarbons having both a double and a triple bond are referred to as "ene-yne-series hydrocarbons". On the other hand, aliphatic hydrocarbons having cyclic compound include various alicyclic compounds free from aromaticity, for example, cyclohexane, decalin, steroids or the like.

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